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Department of Laboratory Medicine
and Pathology

November 3, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on docket 98N-0581

To Whom It May Concern:

Listed below are our comments regarding the document *Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents; Proposed Rule.* Thank you for your consideration of our comments in formulating the final rules.

1. FDA is requesting comment on whether to exempt from testing for evidence of infection due to communicable disease agents listed in § 610.40(a) each donation of dedicated apheresis donors
   We believe that the FDA should revise their requirements to allow testing proposed in § 610.40(a) to be completed once at the beginning of each 30-day period. However, this exemption to testing should also include all other required tests, such as determination of ABO, Rh, red cell antibody screening, and syphilis testing (if that requirement remains in place). We believe that introducing an extended period for testing on only a limited number of tests will introduce the potential for error, in that other tests, which should have been performed, will inadvertently be omitted. The requirement that the exemption should only apply to a dedicated donor should be removed, since administratively it is easy to keep track of whether a test was performed but not why. This comment also impacts the proposed rule for 21 CFR 640.23(a) in Docket No. 98N-0673.

2. Supplementary Information, Section I. Introduction, B. Requirements and Recommendations for Testing Donors of Blood and Blood Components
   In this section the FDA is proposing to: require screening tests for evidence of infection due to communicable disease agent for autologous donations (blood donations intended to be later reinfused into the donor) in order to reduce the risk of transmission of communicable disease by untested units inadvertently entering the blood supply. It is unclear whether the FDA intends to include or exclude units of autologous blood salvaged intraoperatively and returned to the blood bank for storage prior to post-operative reinfusion. If the intent is to exclude, then § 610.40(b) Exceptions, should be revised to state "units of intraoperatively salvaged blood are not required to be tested for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section." If the intent is to include, such units would need to be discarded since it would be essentially impossible to have test results prior to the expiration of these units. In several types of surgery (e.g. total knee arthroplasty) the bulk of the transfusions are given post-operatively, rather than in the operating room. If the intraoperatively salvaged blood requires testing, the regulation will effectively preclude such salvage for these cases.

Sincerely,

S. Breanndan Moore, M.D.
Chair, Division of Transfusion Medicine
cc: Mary Foss
Tania Motschman

98N-0581

C 6

In the following serological picture:

HBsAg - NEGATIVE
HBcAb - POSITIVE
HBcAb IgM - NEGATIVE
HBsAb - POSITIVE

donor has had Hepatitis B infection in the past which has resolved. Non-hepatic tissue from such donor can not transmit Hepatitis B and donor should be considered suitable. It must be mentioned that 95-99% of adults contracting hepatitis B infection progress to complete recovery with development of established protective antibody (HBsAb). Enclosed is a study published in The Lancet in 1974. This study was supported by a grant from National Heart and Lung Institute, Bethesda, Maryland and performed in collaboration with the Blood Bank Department of National Institute of Health

This study examined the risk of transfusing blood containing HBsAb. Since this study was performed prior to Hepatitis B vaccine being available, all donors with positive HBsAb had prior infection with Hepatitis B virus and by definition also had positive HBcAb. The study has found that HBsAb positive blood does not transmit Hepatitis B to the recipients.

Presence of HBcAb (IgG) is not a SCREENING TEST for Hepatitis B infectivity as the proposed rule states, but a HISTORICAL TEST indicating previous infection with Hepatitis B virus which in the vast majority of cases terminates in recovery and development of protective immunity.

Sincerely

Eli Gendler MD
Medical Director
Pacific Coast Tissue Bank

Tillman M. Moore MD
Medical Director
Pacific Coast Tissue Bank

ATTACHMENT

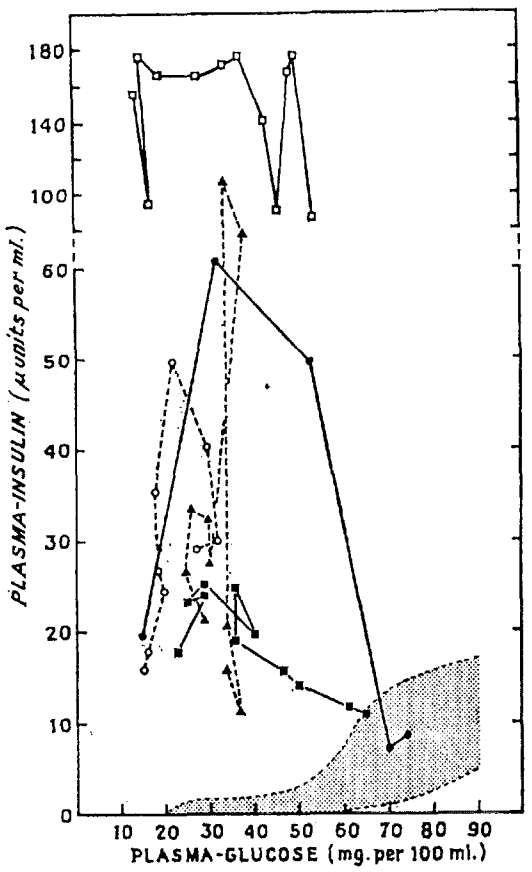

Fig. 4—Five patients with insulinomas in whom there was a temporary rise in plasma-insulin levels in response to fish-insulin-induced hypoglycæmia.

See legend to fig. 2.

which confirmed the diagnosis in the four patients who had normal basal glucose levels after an overnight fast. Although partial suppression of insulin secretion in response to hypoglycæmia was seen in some patients, the plasma-insulin levels remained distinctly abnormal in all the patients studied. In some patients there was a paradoxical increase in insulin secretion during the test. The cause of this is uncertain, but fish insulin contains immunoreactive glucagon, and this may have stimulated insulin secretion.

Hypoglycæmia during a three-day fast has often been used as a diagnostic test for insulinomas, and is an indirect means of demonstrating impaired suppression of insulin secretion. It is not specific unless raised plasma-insulin levels are also demonstrated. Exercise during the fast helps to induce hypoglycæmia, but fish-insulin can produce a more certain fall in plasma-glucose over a shorter period. If spontaneous hypoglycæmia has been documented, a positive fish-insulin suppression test is diagnostic of an insulinoma and a fast is unnecessary.

In a patient in whom fasting hypoglycæmia is suspected as a possible cause of a curious attack, the demonstration of normal suppression of insulin secretion during a fish-insulin test probably excludes the diagnosis of an insulinoma. Stimulation tests for insulinomas are not useful in this context, because false-negative results are common.[5,6] A normal fish-insulin test will not exclude other causes of fasting hypoglycæmia, and only a prolonged fast will definitely do this. However, most of the other causes of fasting hypoglycæmia in adults can be easily excluded by other means. Endocrine deficiencies of the pituitary or adrenal, and cirrhosis, are usually severe and clinically apparent before hypoglycæmia occurs. The hypoglycæmia induced by the fish-insulin test provides a stimulation test for cortisol and growth-hormone secretion, with increased plasma levels at the end of the test.[7] Hypoglycæmia induced by ethanol, sulphonylurea, or other drugs, may be suspected from the history, and self-administration of insulin usually induces circulating insulin antibodies. Sarcomas causing hypoglycæmia are usually large, and can be detected by palpating the abdomen, or by a chest X-ray. Thus a normal fish-insulin suppression test combined with clinical assessment and a few simple tests exclude virtually all causes of fasting hypoglycæmia in adults. These tests can be performed on outpatients, and are useful in situations in which fasting hypoglycæmia is a possible, but improbable, cause of curious attacks.

We thank Prof. P. B. Beeson for his support; the physicians who kindly referred the patients; and Mrs C. Ponsford, Mrs M. Phillips, and Mrs C. Uren for their assistance. Six of the patients with insulinomas were reported in earlier studies performed with Dr N. W. Oakley, Dr. J. D. N. Nabarro, and Miss P. C. Johnson. This study was supported by grants from the British Diabetic Association and Peel Medical Research Trust.

Requests for reprints should be addressed to R. C. T.

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RISK OF TRANSFUSING BLOOD CONTAINING ANTIBODY TO HEPATITIS-B SURFACE ANTIGEN

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Summary 362 blood-transfusion recipients, whose sera were initially negative for hepatitis-B antigen (HB_sAg), were prospectively followed for clinical and serological evidence of exposure to hepatitis-B virus (H.B.V.) and for the development of hepatitis unrelated to H.B.V. Nine

of the donor units received by these patients contained detectable HB_sAg. Of the 362 transfusion recipients, 23 (6%) developed 25 episodes of hepatitis; only 4 of these 25 episodes were serologically related to H.B.V. Based on the absence of antibody to HB_sAg (anti-HB_s) prior to transfusion, 278 of the patients were considered susceptible to H.B.V. infection. Of these susceptible patients, 133 received at least one unit of blood containing anti-HB_s; when compared with the 145 who did not receive anti-HB_s, there was no significant difference in biochemical or overt hepatitis B (3/133 vs. 1/145), in serological response to H.B.V. (5/133 vs. 5/145), or in hepatitis unrelated to H.B.V. (11/133 vs. 6/145). It is concluded that blood containing detectable anti-HB_s carries no increased risk of transmitting hepatitis B compared with blood which lacks this antibody.

Introduction

THE risk of developing post-transfusion hepatitis has been markedly reduced by the adoption of universal testing of donor bloods for hepatitis-B antigen (HB_sAg) and by decreased utilisation of commercial blood.[1] However, despite the exclusion of HB_sAg-positive blood donors, some HB_sAg-positive post-transfusion hepatitis continues to occur.[1-4] This could be due to the administration of HB_sAg or other specific antigens associated with hepatitis-B virus (H.B.V.) in quantities below the threshold of current detection methods.[1-8] HB_sAg could also escape detection if that antigen were complexed to and therefore masked by antibody to it (anti-HB_s). In the latter instance, one might detect only circulating anti-HB_s in blood that is potentially infectious.[9] In addition, since the presence of anti-HB indicates past exposure to the hepatitis-B virus, the finding of this antibody might be just as valid a reason for donor exclusion as is the currently accepted exclusion based upon a history of clinical hepatitis.[10,11]

Despite these theoretical considerations, blood containing anti-HB_s is still transfused and the few studies performed to date have failed to demonstrate an increased infectivity of such antibody-containing blood; the issue, however, is not totally resolved because the number of individuals followed has been small or because the studies have lacked serological data to assess susceptibility to H.B.V.[12-14] Furthermore, the exclusion of donors with anti-HB_s would severely reduce blood availability, since 5–20% of volunteer donors have anti-HB_s detectable by present, sensitive techniques.[10] We have combined data from three prospective studies of post-transfusion hepatitis in order to determine more clearly if donor blood containing anti-HB_s carries a significantly greater risk of transmitting hepatitis B than blood which lacks this antibody.

Patients and Methods

Design of Studies

The studies were performed in three medical centres: the Washington University Medical Center in St. Louis, the Baylor College of Medicine–Ben Taub General Hospital in Houston, and the National Institutes of Health Clinical Center in Bethesda. The designs of these studies have previously been described.[1-4] Patients were assessed at the Washington University and the Ben Taub General Hospital beginning August, 1971, and at the Clinical Center Blood Bank beginning February, 1970. All patients successfully completed a six-month follow-up by November, 1973.

The Washington University study and the Clinical Center Blood Bank study followed cardiovascular-surgery patients, while the Baylor study followed a randomised sample of general-surgery patients who received blood-transfusions at Ben Taub General Hospital. The three studies are very comparable in design and are summarised in table I. All donor units were tested for antigen and antibody, and recipients were followed at least every two weeks for three months and every month thereafter for three months. Washington University patients were followed every two weeks for six months. Patients were excluded if they received transfusions on more than one occasion or if they received blood derivatives other than plasma, red cells, or whole blood.

Definitions

Hepatitis was diagnosed when, between two and twenty-six weeks following transfusion, alanine aminotransferase (S.G.P.T.) and/or aspartate aminotransferase (S.G.O.T.) rose to at least 2 times the upper limit of normal on 2 successive occasions at least a week apart, and when there was no other obvious explanation for the enzyme elevation. *Icterus* was defined as a bilirubin greater than 2 mg. per 100 ml. *Hepatitis B* was diagnosed when, during an episode of hepatitis, HB_sAg was detected, and/or the patient developed antibody seroconversion. *Seroconversion* was the de-novo appearance, and persistence, of anti-HB_s twenty-one or more days after transfusion in a patient having no pre-existing antibody to the hepatitis-B antigen. *Anamnestic response* was a fourfold or greater rise of anti-HB_s occurring within fourteen days following transfusion in a patient with pre-existing antibody. *Serological response only* was defined as seroconversion, or anamnestic response, or development of HB_sAg in a patient who did not develop enzyme elevations indicative of hepatitis. *Exposure* was measured by development of hepatitis B and/or serological response to H.B.V.

Technique

All donors in this study were tested for HB_sAg by counterelectrophoresis[15,16] prior to transfusion. After transfusion, stored sera from these donors were retested by radioimmunoassay. At Washington University and at Baylor subsequent testing was performed by double-antibody radioimmunoassay (R.I.A.-D.A.)[17-19] and by solid-phase radioimmunoassay (Ausria).[20] At the Clinical Center most specimens, but not all, were retested by Ausria. Patients who were HB_sAg-positive prior to transfusion or who received blood containing HB_sAg were excluded from analysis in this report.

Anti-HB_s was measured by R.I.A.-D.A.[18,21] and by passive hæmagglutination (P.H.A.).[22] These methods have recently been compared.[23] Washington University initially tested for anti-HB_s by R.I.A.-D.A. and confirmed positives by P.H.A.; Baylor screened for antibody by P.H.A. and confirmed positives by R.I.A.-D.A. The Clinical Center Blood Bank tested for antibody by R.I.A.-D.A. initially in the study and by P.H.A. later.

Statistical analysis was performed by Dr Marian Fisher of the Biometrics Research Branch, National Heart and Lung Institute, using Fisher's exact test, two tails. Statistical significance in this study is defined as a P value of 0·05 or less.

Results

362 patients whose pre-transfusion sera were all initially HB_sAg-negative were followed for six months after transfusion. Sera from all of their donors were tested for HB_sAg and anti-HB_s. Table I shows the number of patients and the average number of units received per patient at each participating centre. The proportion of donors with antibody ranged from 9% at the Clinical Center to 15% at Ben Taub, whereas the proportion of recipients with pre-transfusion antibody ranged from 10% to 29%.

Table II provides the clinical and serological response to blood-transfusion in the 362 blood recipients. Among these patients, 25 episodes of hepatitis occurred, 4 of which were ascribed to type-B hepatitis. 2 patients had two distinct episodes of hepatitis—a short-incubation, non-type-B, anicteric illness, and a subsequent long-incubation, HB_sAg-positive, icteric illness. 7 additional patients had a serological response to H.B.V. without biochemical evidence of hepatitis; 1 developed HB_sAg alone, 5 had seroconversion, and 1 had an anamnestic response. All 4 cases of HB_sAg-positive hepatitis were icteric compared with only 5 of 21 non-B hepatitis cases. There were no fatalities attributable to hepatitis in any of the patients followed.

TABLE I—CHARACTERISATION OF DONORS AND PATIENTS IN EACH STUDY CENTRE (ALL DONOR UNITS WERE NEGATIVE FOR HB_sAg* AND WERE TESTED FOR ANTI-HB_s)

Participating centre	No. of recipients followed six months	Average no. of donor units transfused per patient	Commercial blood (%)	Donors anti-HB_s positive (%)	Recipients anti-HB_s positive before transfusion (%)
Washington University Medical Center	105	11·3	0	11	22
Baylor-Ben Taub General Hospital	208	2·8	15†	15	29
Clinical Center Blood Bank	49	18·5	0	9	10

* All donor units were tested by counterelectrophoresis prior to transfusion; subsequently at Washington University and at Baylor all units, and at the Clinical Center most units, were retested by radioimmunoassay.

† 15% of the blood was obtained from a commercial blood-bank service but only one-fourth of these donors were paid.

We first analysed the entire recipient population (362 patients) in order to compare the clinical and serological outcome in those who received antibody-containing blood with those who did not (table II). There was no significant difference in measured H.B.V. exposure (5/172 vs. 5/190) nor in hepatitis unrelated to H.B.V. (13/172 vs. 8/190). Patients were then analysed separately according to whether or not they had anti-HB_s prior to transfusion. 278 recipients did not have pre-existing anti-HB_s; 145 of these recipients received only blood which lacked anti-HB_s while 133 received at least one unit of blood containing anti-HB_s. When these groups were compared there was again no significant difference in measured H.B.V. exposure (5/145 vs. 5/133), in hepatitis B (1/145 vs. 3/133), or in hepatitis unrelated to H.B.V. (6/145 vs. 11/133).

84 patients had antibody to HB_sAg at the time of transfusion. 4 of these patients developed hepatitis, but none was serologically related to H.B.V. An anamnestic serological response to H.B.V. was observed in only 1 of the recipients with pre-existing anti-HB_s; that patient received blood containing anti-HB_s.

Among the 362 recipients in this study there were 21 episodes of hepatitis in which neither HB_sAg nor anti-HB_s could be demonstrated. These non-type-B cases showed no significant association with the presence or absence of pre-existing anti-HB_s in the recipient or with the presence or absence of anti-HB_s in donor blood.

35 additional susceptible patients were followed by the Clinical Center Blood Bank. They were not included in the preceding analysis because greater than 90%, but not all, of their donor sera were tested for anti-HB_s.

All donors were tested for HB_sAg and were found to be negative. Each of these 35 patients received at least one unit of blood containing anti-HB_s. A negative control group for these patients cannot be presented because of the uncertain antibody status of untested donors. None the less, among these 35 additional recipients of blood containing anti-HB_s, none developed type-B hepatitis or serological response to H.B.V.; 2 developed hepatitis unrelated to H.B.V.

Discussion

Seeff et al.,[14] in a preliminary report of a study of over 2000 blood recipients, found that the risk of

TABLE II—CLINICAL AND SEROLOGICAL RESPONSE OF RECIPIENTS TO BLOOD WHICH CONTAINED OR LACKED ANTI-HB_s

Pre-transfusion serological status of recipient	Total no. of recipients	Donor blood contains: HB_sAg	Donor blood contains: Anti-HB_s	No. of recipients	Total cases of hepatitis	Confirmed exposure to H.B.V.: Total hepatitis-B cases*	Serological response only: HB_sAg	Serological response only: Anti-HB_s	Total hepatitis-B exposure	Total non-type-B hepatitis*
No HB_sAg or anti-HB_s	278	—	—	145	7†	1 (1)†	1	3	5	6 (0)†
		—	—	133	14†	3 (3)†	0	2	5	11 (4)†
Pre-existing anti-HB_s only	84	—	—	45	2	0	0	0	0	2 (1)
		—	—	39	2	0	0	1	1	2 (0)
Totals	362			362	25	4 (4)	1	6	11	21 (5)
							7			

* Numbers in parentheses indicate numbers of total cases which were icteric.

† 2 episodes of hepatitis were diagnosed in each of 2 patients; the first episode in each patient was non-type-B and the second was type-B hepatitis.

developing overt or biochemical hepatitis B after receiving at least one unit of blood containing anti-HB_s (1·4%) was not significantly greater than the risk after receiving blood without detectable antigen or antibody (0·6%); both groups had significantly less hepatitis than a third group receiving blood which contained only HB_sAg (13·7%).

Goldfield et al.[24] prospectively studied 29 recipients of anti-HB_s-containing, HB_sAg-negative blood and 103 controls who received blood with neither anti-HB_s nor HB_sAg; recipients of antibody-containing blood did not demonstrate an increased frequency of post-transfusion hepatitis. Gocke and Panick[12] compared 37 recipients of anti-HB_s-containing blood with 136 recipients of anti-HB_s-negative blood, and concluded that antibody-containing blood carried no increased risk of transmitting hepatitis B. In all three studies, the pre-transfusion antibody status of the recipients was not stated and therefore their presumed susceptibility to H.B.V. was unknown. In addition, the post-transfusion serological response of the patients was not given and thus the ability of anti-HB_s-containing blood to elicit an HB_sAg response without hepatitis or to cause seroconversion without disease could not be ascertained.

The present study provides data not only on the development of hepatitis, but also on the development of serological response to H.B.V., and permits analysis of these data in terms of whether or not the recipient was initially susceptible to H.B.V. as judged by the presence of anti-HB_s in the serum before transfusion. When the entire patient population was analysed, neither the risk of hepatitis B nor the frequency of serological exposure to H.B.V. was significantly greater in those transfused with anti-HB_s than in those who did not receive antibody-containing blood. A similar lack of statistical association was observed when only those patients without pre-existing antibody (presumably susceptible patients) or when only patients with pre-existing antibody were analysed.

No cases of biochemical or overt hepatitis B occurred among the 84 recipients with pre-existing anti-HB_s in contrast to the 4 cases which developed among the 278 presumably susceptible recipients. Although these differences are not statistically significant, they are consistent with previous studies[25,26] which indicate that anicteric or icteric hepatitis B in patients with pre-existing anti-HB_s is extremely unusual.

The total hepatitis risk for patients in this study was 6·4%. Only 1·1% of recipients developed hepatitis B; hence only 16% of the total hepatitis was related to H.B.V. As expected, there was no relationship between the frequency of non-type-B hepatitis and the presence of anti-HB_s in either the donor or the recipient prior to transfusion.

We conclude from our data and other studies that the risk of exposure to hepatitis-B virus or of development of HB_sAg-positive hepatitis following transfusion of anti-HB_s-containing blood is not significantly greater than that observed following the transfusion of blood which lacks detectable anti-HB_s. The data do not support exclusion of donor blood containing anti-HB_s.

This work was supported in part by contracts NIH-NHLI-70-2231 and NIH-NHLI-71-2353 from the National Heart and Lung Institute. We thank Miss Patricia Clay, Mr Jerry Chervitz, Mrs Loma Coday, Mrs Susan Fallek, Mr James McAdam, Mrs Shirley Snowe, Ms Karen Landry, Ms Melinda Freeman, Dr Marian Fisher, and Dr Robert Purcell for technical assistance.

Requests for reprints should be addressed to J. M. W., Building 31, Room 5A-11, Blood Resources Branch, Division of Blood Diseases and Resources, National Heart and Lung Institute, Bethesda, Maryland 20014, U.S.A.

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SEASONAL OCCURRENCE OF COMPLEX VENTRICULAR SEPTAL DEFECT

KENNETH J. ROTHMAN DONALD C. FYLER

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Summary The seasonal occurrence of births of children with ventricular septal defects (V.S.D.) was examined for a series of 302 cases from New England. The overall series showed a moderate peak in the summer, which was entirely attributable to a strong tendency for complex V.S.D. to occur in summer. Complex V.S.D. occurred 4·4 times more frequently in urban counties than rural counties, and the seasonal trend was strongest in urban areas. The seasonal peak was not associated with birth-weight,

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